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91. The method of any one of claims 1, 55, 60, or 75, wherein said solid phase surface is a tissue culture dish.

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92. The method of any one of claims 1, 55, 60, or 75, wherein the anti-CD3 antibody and the anti-CD28 antibody are immobilized on the solid phase surface via a covalent modification.

93. The method of any one of claims 1, 55, 60, or 75, wherein the anti-CD3 antibody and the anti-CD28 antibody are immobilized on the solid phase surface via an avidin-biotin complex.

94. The method of any one of claims 1, 55, 60, or 75, wherein the anti-CD3 antibody and the anti-CD28 antibody are directly immobilized on the solid phase surface.

REMARKS

Claims 1 and 55-86 are pending in the application. Claims 56-59, 61-74, and 76-86 have been canceled without prejudice, claims 1, 55, 60, and 75 have been amended, and new claims 87-94 have been added. Accordingly, claims 1, 55, 60, 75 and 87-94 are currently pending. For the Examiner's convenience all of the pending claims are set forth in Appendix A.

Support for the amendments to the claims and newly added claims 87-94 may be found throughout the specification, including the originally filed claims. Specifically, support for the amendments to claims 1, 55, 60, and 75 may be found at, for example, page 35, lines 1-2 of the specification. Support for new claims 87 and 88 may be found at, for example, page 7, lines 27-28 and page 23, line 21, through page 24, line 29 of the specification. Support for new claim 89 may be found at, for example, page 3, line 21 of the specification. Support for new claim 90 may be found at, for example, page 13, line 37 of the specification. Support for new claim 91 may be found at, for example, page 14, line 20 of the specification. Support for new claim 92 may be found at, for example, page 17, line 11 of the specification. Support for new claim 93 may be found at, for example, page 14, lines 12-17 of the specification. Support for new claim 94 may be found at, for example, page 16, line 5 of the specification.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned "Version With Markings to Show Changes Made".

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 59, 64-74, 79, 81, 84 and 86 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 59, 64-74, 79, 81, 84 and 86 under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention." In particular, the Examiner is of the opinion that

[w]ith respect to methods of downregulating CXCR4 recited in claims 65-74, 79 and 84; Figure 4 and Example 7 disclose that the levels of mRNA for *CXCR4* are not downregulated after treatment of T cells with anti-CD28 antibody, rather CXCR4 mRNA levels *increase* after stimulation. Furthermore, the specification discloses that the infectivity of a CXCR4-dependent T -tropic virus is not blocked (e.g., Example 3 and figure 1). Therefore, the specification as-filed does not provide enabling support for the instant limitation of decreasing CXCR4 expression *in vitro*.

With respect to claims 59, 64, 69, 74, 81 and 86, the Examiner is of the opinion that

the specification discloses on page 36 at lines 11-13 that *co-immobilization* of the anti-CD28 antibody with an anti-CD3 antibody is required for resistance to the M-tropic (i.e., CCR5-dependent) HIV isolate. Furthermore, the specification on page 35 at line 29 explicitly states that *soluble* anti-CD28 renders T cells sensitive to infection with M-tropic virus; indicating that CCR5 expression is not downregulated. Smithgall et al. (AIDS Res. and Human Retroviruses, 11:885-892 1995, IDS #DK) have also observed that *soluble* anti-CD28 increase cell sensitivity to HIV infection (e.g., "Abstract" and Figure 2). Similar observations have been made by Pinchuk et al. (Immunity 1:317-325 1994, IDS #00; e.g. "Abstract" and Figure 3D). Therefore, the specification as-filed does not provide enabling support for the instant limitation of *soluble* anti-CD28 antibodies. Given

a disclosure that *soluble* anti-CD28 *increases* sensitivity to viral infection; the skilled artisan would not reasonably expect that expression of CCR5 would be downregulated by treatment with *soluble* anti- CD28. Likewise, given *in vitro* examples indicating an *increase* in expression of CXCR4 mRNA and the lack of objective evidence supporting a reasonable expectation that the outcome of the treatment would be different *in vivo*; the skilled artisan would not reasonably expect that CXCR4 expression would be downregulated either *in vitro* or *in vivo*. In both cases the lack of established protocols thus indicate a lack of predictability in the art to which the invention pertains. Therefore, absent a specific and detailed description in Applicant's specification of how to effectively practice the claimed methods, and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for downregulating CXCR4 expression; undue experimentation would be required to practice the claimed methods with a reasonable expectation of success.

Applicants respectfully submit that the foregoing rejection has been rendered moot in view of the amendments to the claims. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing 35 U.S.C., section 112, first paragraph rejection.

The amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 1, 55-64, 75-78, 80-83 and 85-86 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1, 55-64, 75-78, 80-83 and 85-86 under 35 U.S.C. §112, first paragraph because, according to the Examiner, “*the specification, while being enabling for a method of downregulating HIV-1 fusion cofactor expression comprising contacting the T cell with co-immobilized anti-CD3 and anti-CD28; does not reasonably provide enablement for either the full scope of compounds comprising a CD28 ligand; or for anti-CD28 in the absence of anti-CD3.*” (*Emphasis added*). In particular, the Examiner is of the opinion that

[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention

commensurate in scope with these claims. The specification discloses on page 6 at lines 4-7 that CD28 ligands include antibodies to CD28 as well as the natural ligands B7.1 (CD80) and B7.2 (CD86). Carroll et al. (*Immunol.* 10: 195-202 1998) review the art recognized interaction of B7.1 and B7.2 with another molecule, CTLA-4 and discuss the observations that CTLA-4 ligation inhibits T cell signaling (see "the CD28/CTLA-4/B7 co-stimulation pathway" on pages 195-196). Carroll et al. also teach that CTLA-4 ligation *increases* CCR5 expression, even in the presence of CD28 stimulation (e.g. page 198, bridging paragraph of columns I and 2). Thus the CD28 ligands B7.1 and B7.2 would be expected to *increase* CCR5 expression because they bind both CD28 and CTLA4, but the CTLA4 effect is dominant (summarized at page 199, in "CD28/B7 co-stimulation pathways and HIV-I infection *in vivo*", 2nd paragraph). The specification discloses on page 36 at lines 11-13 that co-immobilization of the anti-CD28 antibody with an anti-CD3 antibody is required for resistance to the M-tropic (i.e., CCR5-dependent) HIV isolate. The specification on page 35 at line 29 also explicitly states that *soluble* anti-CD28 renders T cells sensitive to infection with M-tropic virus; indicating that CCR5 expression is not downregulated. Insufficient evidence is provided that immobilized anti-CD28 by itself downregulates CCR5 expression, since it appears that all experiments were carried out in the presence of immobilized anti-CD3.

The Examiner further states that

[r]easonable correlation must exist between the scope of the claims and scope of enablement set forth. The data disclosed in the specification as-filed and the teachings of Carroll et al. indicate that there are several non-functioning embodiments within the scope of the claims. Therefore, the experimentation left to those skilled in the art to identify other CD28 ligands that would function in the recited methods is unnecessarily, and improperly, extensive and undue. Likewise, the experimentation left to those skilled in the art to identify other formulations in which an anti-CD28 antibody would function in the claimed methods is unnecessarily, and improperly, extensive and undue. Applicant should limit "comprising contacting the T cell with a CD28 ligand" to contacting the T cell with *co-immobilized anti-CD28 and anti-CD3*, as disclosed in the specification as-filed, to obviate this rejection.

Applicants respectfully submit that the foregoing rejection has been rendered moot in view of the amendments to the claims. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing 35 U.S.C., section 112, first paragraph rejection.

The amendments to and/or cancellation of the claims should in no way be construed as an

acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 1 and 55-86 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1 and 55-86 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

With regard to claims 1 and 55-86, the Examiner is of the opinion that these claims

are indefinite in their recitation of "downregulating (cofactor/CCR5/CXCR4) expression" because it is ambiguous as to whether mRNA or protein expression is downregulated. The specification on page 3 at lines 6-8 indicates techniques used for monitoring levels of mRNA and protein has been shown to be discordant for CXCR4 Riley et al. (J. virol. 72:8273-8280 1998; see page 8278, 2nd paragraph). Therefore, without an identification of whether "downregulating (cofactor/CCR5/CXCR4) expression" refers to mRNA or protein, the phrase is ambiguous, especially with respect to CXCR4.

Applicants respectfully traverse the foregoing rejection on the grounds that the present invention is claimed in clear and concise language such that the ordinarily skilled artisan can delineate the metes and bounds of the claimed invention. The "[d]efiniteness of claim language must be analyzed, not in vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in pertinent art at the time the invention was made." M.P.E.P. § 2173.02.

First and foremost, the phrase "downregulating (cofactor/CCR5/CXCR4) expression" is well known and understood in the art. As evidenced by, for example, U.S. Patent Nos. 5,962,635 (e.g., claim 3) and 5,837,694 (e.g., claim 4) submitted herewith as Appendices B and C, respectively, this phrase is understood to mean downregulating mRNA and/or protein expression. Moreover, Applicants' specification teaches that modulation (e.g., downregulation)

of cofactor expression may occur and be monitored at both the mRNA and/or the protein level (see page 27, line 31, through page 29, line 31 of the instant specification).

In view of the foregoing, Applicants respectfully submit that the ordinarily skilled artisan would understand the phrase "downregulating (cofactor/CCR5/CXCR4) expression" to mean downregulating mRNA and/or protein expression. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, second paragraph rejection.

Regarding claims 85 and 86, the Examiner states that these claims

recite the limitation "method of claim 3". There is insufficient antecedent basis for this limitation in the claim. It appears that the method of claim 83 is intended.

Applicants respectfully submit that the foregoing rejection has been rendered moot in view of the cancellation of claims 85 and 86. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing 35 U.S.C., section 112, second paragraph rejection.

Rejection of Claims 1,55-58, 82-83 and 85 under 35 U.S.C. §102(a)

The Examiner has rejected claims 1,55-58,82-83 and 85 under 35 U.S.C. §102(a) as being anticipated by Levine *et al.* (1996) *Science* 272:1939-1942. The Examiner relies on Levine *et al.* for teaching "a method for downregulating HIV fusion co-factor expression in a T cell by contacting the T cell with co-immobilized anti-CD3/anti-CD28 *in vitro* (see entire document)" and for teaching that "the T cells are activated (e.g., Figure 1A)." In particular, the Examiner is of the opinion that

[a]lthough downregulation of the HIV-I fusion co-factor CCR5 is not explicitly demonstrated, the use of identical methodology as that disclosed in the specification as-filed indicates that downregulation of CCR5 would be inherent; as indicated by the resistance of the T cells to infection with the M-tropic (CCR5-dependent) HIV-1 strain. When a claim recites using an old composition or structure (e.g. immobilized anti-CD3/anti-CD28 antibodies) and the use is directed to a result or property of that composition or structure (downregulation

ofCCRS), then the claim is anticipated. See MPEP 2112.02. Also, see Ex Darte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/BioDhile International Com. V. MilWYm, 52 USPQ2d 1303 (Fed. Cir. 1999); ~ Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999). Applicant is reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.0 I (d) and MPEP 2112:- 2113 for case law on inherency.

Based on information and belief, it is the understanding of the undersigned Attorney that Bruce L. Levine, Joseph D. Mosca, Maryanne T. Vahey, Linda L. Jagodzinski, Kenneth F. Wagner, Douglas L. Mayers, Donald S. Burke and Owen S. Weislow, who are co-authors with the inventors in the Levine *et al.* paper, are *not* co-inventors of the subject matter described and claimed in the above-identified application. As such, the Levine *et al.* paper represents Applicants' own work, published within the year before the filing of the present application, and cannot be used against Applicants under 35 U.S.C. § 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1958). Applicants' Attorney is confirming this understanding with the presently named Applicants.

Rejection of Claims 1, 55-58, 60-63, 75-78, 80, 82-83 and 85 under 35 U.S.C. §102(e)

The Examiner has rejected claims 1, 55-58, 60-63, 75-78, 80, 82-83 and 85 under 35 U.S.C. §102(e) as being anticipated by Chang (U.S. Patent No. 6,129,916). The Examiner relies on Chang for teaching "a method of activating T cells *in vivo* by contacting the T cells with co-immobilized anti-CD3/anti-CD28 (see entire document, especially claims 1-2 and columns 11-12)" and "[t]he use of such conjugates *in vitro* ... (e.g., column 5, especially lines 31-37)." In particular, the Examiner is of the opinion that

[a]lthough downregulation of HIV-1 fusion co-factors including CCR5 is not explicitly demonstrated, the use of *in vivo* methodology equivalent to that disclosed in the specification as-filed for *in vitro* experiments indicates that downregulation of CCR5 would be an inherent outcome of these methods. When a claim recites using an old composition or structure (e.g. immobilized anti-CD3/anti-CD28 antibodies) and the use is directed to a result or property of that composition or structure (downregulation of CCR5), then the claim is anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corn. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir.

1999); Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999). Applicant is reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01 (d) and MPEP 2112 -.2113 for case law on inherency.

Applicants respectfully traverse the foregoing rejection for the following reasons. The pending claims are directed to methods for downregulating HIV-1 fusion cofactor expression in a T cell by contacting the T cell with a solid phase surface comprising an anti CD28 antibody and an anti-CD3 antibody.

For a prior art reference to anticipate in terms of 35 U.S.C. § 102 a claimed invention, the prior art must teach *each and every element* of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Moreover, with regard to inherency, “a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination.” *In re Newell*, 891 F.2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989).

Applicants respectfully submit that Chang does not teach or suggest the methods of the pending claims. Chang discloses that “in one embodiment of the invention, an anti-CD3 binding molecule and an anti-CD2, anti-CD4, anti-CD5, anti-CD8, anti-CD28 or other binding molecule specific for T cells, is conjugated to a polymer backbone, a liposome, or a microbead” and that “[t]he polymerized or immobilized pairs of binding molecules can then be used to activate T cells *in vivo*” (column 12, lines 7-13). There is no teaching or suggestion in Chang that would motivate an ordinarily skilled artisan to select antibodies that bind CD3 and antibodies that bind CD28 among the list of antibodies which are taught as equally useful for activating T cells *in vivo*.

With regard to *in vitro* methods, Chang, at most, teaches that the conjugates can be used diagnostically, to determine the number or proportion of T cells in a fluid sample (see e.g., column 5, lines 32-36). For this use, Chang teaches that the conjugates of the invention can be used in standard lymphocyte proliferation assays, such as an [³ H]-thymidine incorporation

assay.

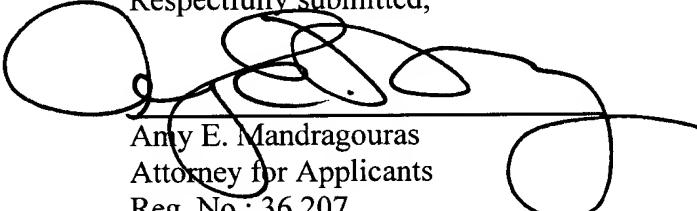
Nowhere does Chang teach or suggest a method for downregulating HIV-1 fusion cofactor expression in a T cell by contacting the T cell with a solid phase surface comprising an anti CD28 antibody and an anti-CD3 antibody, as required by Applicants' pending claims.

In summary, since Chang fails to teach or suggest each and every element of the pending claims, Applicants respectfully request that this section 102(e) rejection, be reconsidered and withdrawn.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. **(Amended)** A method for downregulating HIV-1 fusion cofactor expression in a T cell, comprising contacting the T cell with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody CD28 ligand *in vitro*, thereby downregulating HIV-1 fusion cofactor expression in the T cell.

55. **(Amended)** A method for downregulating CCR5 expression in a T cell, comprising contacting the T cell with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody CD28 ligand *in vitro*, thereby downregulating CCR5 expression in the T cell.

60. **(Amended)** A method for downregulating CCR5 expression in a T cell, comprising contacting the T cell with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody CD28 ligand *in vivo*, thereby downregulating CCR5 expression in the T cell.

75. **(Amended)** A method for downregulating HIV-1 fusion cofactor expression in a T cell, comprising contacting the T cell with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody CD28 ligand *in vivo*, thereby downregulating HIV-1 fusion cofactor expression in the T cell.

APPENDIX A

1. A method for downregulating HIV-1 fusion cofactor expression in a T cell, comprising contacting the T cell with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody *in vitro*, thereby downregulating HIV-1 fusion cofactor expression in the T cell.

55. A method for downregulating CCR5 expression in a T cell, comprising contacting the T cell with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody *in vitro*, thereby downregulating CCR5 expression in the T cell.

60. A method for downregulating CCR5 expression in a T cell, comprising contacting the T cell with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody *in vivo*, thereby downregulating CCR5 expression in the T cell.

75. A method for downregulating HIV-1 fusion cofactor expression in a T cell, comprising contacting the T cell with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody *in vivo*, thereby downregulating HIV-1 fusion cofactor expression in the T cell.

87. The method of any one of claims 1, 55, 60, or 75, wherein the anti-CD3 antibody is an anti-human CD3 monoclonal antibody.

88. The method of any one of claims 1, 55, 60, or 75, wherein the anti-CD28 antibody is an anti-human CD28 monoclonal antibody.

89. The method of any one of claims 1, 55, 60, or 75, wherein said solid phase surface is a bead.

90. The method of claim 89, wherein the bead is a magnetic immunobead.

91. The method of any one of claims 1, 55, 60, or 75, wherein said solid phase surface is a tissue culture dish.

92. The method of any one of claims 1, 55, 60, or 75, wherein the anti-CD3 antibody and the anti-CD28 antibody are immobilized on the solid phase surface via a covalent

modification.

93. The method of any one of claims 1, 55, 60, or 75, wherein the anti-CD3 antibody and the anti-CD28 antibody are immobilized on the solid phase surface via an avidin-biotin complex.

94. The method of any one of claims 1, 55, 60, or 75, wherein the anti-CD3 antibody and the anti-CD28 antibody are directly immobilized on the solid phase surface.